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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/634,537	08/04/2003	Kyriacos C. Nicolaou	TSRI 904.1	6050

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EXAMINER	
STOCKTON, LAURA	

ART UNIT	PAPER NUMBER
1626	

DATE MAILED: 07/08/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/634,537	NICOLAOU ET AL.	
	Examiner	Art Unit	
	Laura L. Stockton, Ph.D.	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 May 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,9,11-18 and 27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,9,11-18 and 27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

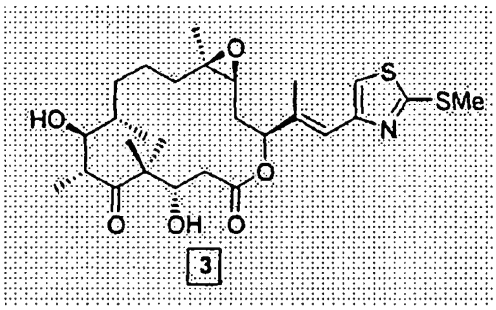
1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/21/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-3, 9, 11-18 and 27 are pending in the application.

Election/Restrictions

Applicants' election without traverse of Group I, and the species of claim 14 which corresponds to compound 3 of Figure 1A (reproduced below), in the reply filed on May 20, 2005 is acknowledged.



Applicants cancelled claims 4-8, 10 and 19-26 as being directed to non-elected subject matter.

Information Disclosure Statement

The Information Disclosure Statement filed on April 21, 2005 has been considered by the Examiner.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 11 and 12 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. § 112, first paragraph, have been described. They are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,
5. the presence or absence of working examples,
6. the breadth of the claims,
7. the quantity of experimentation needed, and
8. the level of the skill in the art.

The nature of the invention

Applicants are claiming a pharmaceutical composition for treating a proliferative disease by administering a compound of claims 1-3, 9, 13-18 and 27). See claim 11. From the reading of the specification, it appears that Applicants are asserting

that the embraced compounds, because of their mode action, would be useful for treating all proliferative diseases.

The state of the prior art and the predictability or lack thereof in the art

The state of the prior art is that cancer therapy, for example, remains highly unpredictable. The various types of cancers have different causative agents, involve different cellular mechanisms, and consequently, differ in treatment protocol. It is known (see Golub et al., Science, Vol. 286, October 15, 1999, pages 531-537) that the challenge of cancer treatment has been to target specific therapies to pathogenetically distinct tumor types, to maximize efficacy and minimize toxicity. Cancer classification has been based primarily on morphological appearance of the tumor and that tumors with similar histopathological appearance can follow significantly different clinical courses and show different responses

to therapy (Golub et al., Science, Vol. 286, October 15, 1999, pages 531-537). There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face.

The amount of direction or guidance present and the presence or absence of working examples

Pages 11-14, under "Chemical biology", of the instant specification discusses the cytotoxicity being evaluated on ovarian cell lines and human epidermoid cell lines. That a single class of compounds can be used to treat all diseases embraced by the claims is an incredible finding for which Applicants have not provided supporting evidence. Applicants has not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use for

treating all proliferative diseases by administering the instant claimed compounds.

The breadth of the claims

The breadth of the claims is treating all proliferative diseases generically embraced in the claim language.

The quantity of experimentation needed

The nature of the pharmaceutical arts is that it involves screening *in vitro* and *in vivo* to determine which compounds exhibit the desired pharmacological activities for each of the diseases instantly claimed. The quantity of experimentation needed would be undue when faced with the lack of direction and guidance present in the instant specification in regards to testing all diseases generically embraced in the claim language, and when faced with the unpredictability of the pharmaceutical art. Thus, factors such as "sufficient working examples", "the level of skill in the art" and predictability, etc. have been

demonstrated to be sufficiently lacking in the instant case for the instant method claims.

The level of the skill in the art

Even though the level of skill in the pharmaceutical art is very high, based on the unpredictable nature of the invention and state of the prior art and lack of guidance and direction, one skilled in the art could not use the claimed invention without undue experimentation.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 13-18 and 27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim

the subject matter which applicant regards as the invention.

In claim 13, an "and" is needed before the last substituent defining the "R" variable to establish proper Markush language.

Claim 27 does not conform to M.P.E.P. 608.01(m) since each claim must end with a period and thereby establishing that no other subject matter is missing from the claim.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-3, 9, 11-14 and 27 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 and 9 of copending Application No. 10/732,698 and claims 11-18 and 21 of copending Application No. 10/227,073. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claimed compounds are generically described in 10/732,698. See, for example, claim 4 in 10/732,698.

The indiscriminate selection of "some" among "many" is *prima facie* obvious, *In re Lemin*, 141 USPQ 814 (1964). The motivation to make the claimed compounds

derives from the expectation that structurally similar compounds would possess similar activity (e.g., cytotoxic agents).

The difference between the compounds in 10/227,073 and the instant claimed compounds is that of a hydrogen versus a methyl group at the C12 position. It is well established that the substitution of methyl for hydrogen on a known compound is not a patentable modification absent unexpected or unobvious results. *In re Wood*, 199 U.S.P.Q. 137 (C.C.P.A. 1978) and *In re Lohr*, 137 U.S.P.Q. 548, 549 (C.C.P.A. 1963). Further, to those skilled in chemical art, one homologue is not such an advance over adjacent member of series as requires invention because chemists knowing properties of one member of series would in general know what to expect in adjacent members. *In re Henze*, 85 USPQ 261 (1950).

The motivation to make the claimed compounds derives from the expectation that structurally similar

compounds would possess similar activity (ie., cytotoxic activity). Alternatively, see where 10/732,698 teach the interchangeability of hydrogen and methyl at the C12 position.

One skilled in the art would thus be motivated to prepare compounds embraced by 10/732,698, or alternatively, a homolog of 10/227,073, to arrive at the instant claimed compounds with the expectation of obtaining additional beneficial compounds which would be useful as a cytotoxic agent. The instant claimed invention would have been suggested and therefore, obvious to one skilled in the art.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 11-14 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 4, 6-8 and 12-17 of U.S. Patent No. 6,531,497. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claimed compounds are generically described in U.S. Patent No. 6,531,497. See, for example, claim 17 in the patent.

The indiscriminate selection of "some" among "many" is *prima facie* obvious, *In re Lemin*, 141 USPQ 814 (1964). The motivation to make the claimed compounds derives from the expectation that structurally similar compounds would possess similar activity (e.g., cytotoxic agents).

One skilled in the art would thus be motivated to prepare compounds embraced by U.S. Patent No. 6,531,497 to arrive at the instant claimed compounds with the expectation of obtaining additional beneficial compounds which would be useful as a cytotoxic agent.

The instant claimed invention would have been suggested and therefore, obvious to one skilled in the art.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 11-14 are rejected under 35 U.S.C. 102(b) as being anticipated by Nicolaou et al. {WO 99/67252}.

Nicolaou et al. disclose the compound of Example 6(ix) on page 58, which is the same compound listed in instant claim 14 {CA Registry No. 252981-48-9}.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3, 9, 11-14 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vite et al. {WO 99/54318}, Nicolaou et al. {WO 99/67252} and Klimko {WO 2003/026744}, each taken alone or in combination with each other.

Determination of the scope and content of the prior art (MPEP §2141.01)

Applicants claim analogs of epothilone. Vite et al. (pages 1, 2 and 7-10; and especially Example 1 on page 16), Nicolaou et al. (pages 2-4, 26, 29 and 30; and especially the compound of Example 6(ix) on page 58) and Klimko (formula I, pages 5-8 and 11-13; and

especially Compound 2 on page 7) each teach analogs of epothilone which are either structurally the same as (see above 102 rejection) or structurally similar to the instant claimed compounds.

Ascertainment of the difference between the prior art and the claims (MPEP §2141.02)

The difference between some of the compounds of the prior art and the compounds instantly claimed is that the instant claimed compounds are generically described in the prior art.

Finding of prima facie obviousness--rational and motivation (MPEP §2142-2413)

The indiscriminate selection of "some" among "many" is *prima facie* obvious, In re Lemin, 141 USPQ 814 (1964). The motivation to make the claimed compounds derives from the expectation that structurally similar compounds would possess similar activity (e.g., cytotoxic agents).

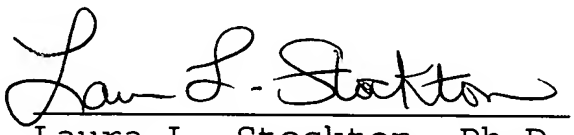
One skilled in the art would thus be motivated to prepare compounds embraced by the prior art to arrive at the instant claimed compounds with the expectation of obtaining additional beneficial compounds which would be useful as a cytotoxic agent. Since each of the prior art references teach analogs of epothilone which are structurally similar to each other, the combination of the prior art references would also teach the instant claimed invention. The instant claimed invention would have been suggested and therefore, obvious to one skilled in the art. A strong case of *prima facie* obviousness has been established.

The species of claim 14, which corresponds to compound 3 of Figure 1A, is not allowable over the art of record (see WO 99/67252).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Laura L. Stockton whose telephone number is (571) 272-0710. The examiner can normally be reached on Monday-Friday from 6:15 am to 2:45 pm. If the examiner is out of the Office, the examiner's supervisor, Joseph McKane, can be reached on (571) 272-0699.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

The Official fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.



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July 7, 2005